Trustworthiness in Medical Product Question Answering by Large Language Models

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ABSTRACT

Large language models (LLMs) have achieved remarkable progress in recent years. These models have the capability to answer complex questions about medical disorders, their pathophysiology, etiology and corresponding interventions. However, when providing information about medical products and treatments, it is important to ensure that models respond reliably with factually correct information that adheres to product labels, and do not produce factual errors in which a claim contradicts established ground-truth knowledge. To this end, in this paper we propose an evaluation method to determine whether claims in LLM responses to questions about medical products are supported by FDA-approved product information.

KEYWORDS

Large Language Model, Evaluation, Medical, Trustworthiness.

1 INTRODUCTION

Recent advancements in generative artificial intelligence have led to the development of large language models (LLMs) capable of processing and generating text with human-like performance. These include open-source models such as Llama [80, 81], and commercial models such as OpenAI's ChatGPT [62] or Anthropic's Claude [5, 7]. These generalist models have achieved impressive results on varied benchmarks including question answering [10, 43, 49, 50, 63, 87]. In healthcare, they have the demonstrated remarkable capabilities in a number of complex expert tasks (e.g. providing differential diagnoses [39], summarizing charts [85], medical image analysis [2, 38], etc.) and shown potential to democratize medical knowledge and facilitate access to healthcare [25]. To this end, progress towards specialized medical LLMs advances rapidly [23, 70, 82, 86]. Fueled by their vast promise, both generalist and specialized LLMs are starting to be adopted in the real-world clinical setting to streamline clinical and administrative tasks [19, 56, 64, 72, 100], and a growing number of clinicians report using LLMs in their clinical practice or education [17, 54, 78, 79].

While LLMs hold vast promise and their capabilities are evolving at a breathtaking speed, their rapid adoption also introduces concerns about their trustworthiness [76]. Specifically, they can hallucinate and produce factual errors in which a claim in the response contradicts established ground-truth knowledge [3, 41, 76], despite appearing plausible and confident. In the medical context, incorrect information can pose significant risk to public health, and cause harm to individuals and organizations [1, 4, 9, 37, 44, 57, 90]. This issue is exacerbated by the potential for patients to use LLMs as a source of medical information, as they may rely wholly on an them for prognosis and treatment, thereby reducing or eliminating reliance on appropriate professional medical judgement and support [90]. Since incorrect information may be indistinguishable from factually accurate responses, patients may be provided with incorrect information. Hence, LLMs have the potential to result in patient harm and lead to severe health consequences, if not adequately deployed with robust guardrails and quality controls.

Given the real-life risks to public health of incorrect health-related information, it is paramount that LLMs are evaluated thoroughly prior to deployment. Even if model developers issue warnings of the potential limitations of LLMs, their misuse can still pose risks [90]. Hence, the development of methods to evaluate the answers of LLMs to medical questions is not just of academic interest but of great practical importance.

While previous works have evaluated the quality of LLMs responses to biomedical and clinical knowledge questions [12, 16, 22, 64, 73], in this work we focus into an overlooked issue that impacts most LLMs, that is, the potential to provide potentially harmful information about medical products, specifically drugs. Traditionally, specialized ML models have been trained to address a specific task using highly domain and problem-specific training data [21]. However, LLM models are trained on much more broadly available generalist datasets [51] with less hands-on human oversight in their development. Therefore, they can learn complex unvetted relationships from the training data and produce outputs about medical products that do not strictly adhere to the approved product labels. Promoting a medical product for anything other than its approved use, often denoted *off-label promotion*, can be unsafe if not done with adequate professional supervision [83]. Therefore, it is preferred that LLMs provide information that adhere to the approved labeling documents [11, 45, 48, 53, 75, 83, 84].

To avoid this issue, building upon previous work on factuality evaluation of LLM responses [47, 58, 88], we propose a method to evaluate if LLM responses strictly adhere to FDA product labels (Sec.3). Our method uses a language model to first decompose a long-form response into individual claim. Then, each claim is evaluated to determine if it relates to one of the standardized FDA labeling document sections. Claims that relate to the labeling documents are fact-checked by comparing it against the corresponding labeling document to determine whether the claim is supported. We demonstrate this methodology using synthetic user questions and LLM responses from Claude 3 [5–7]. While many prior works have evaluated the factiality of LLM responses, to our knowledge this is the first work focused on evaluating medical product question answers and ensuring adherence to the information in the labeling documents.

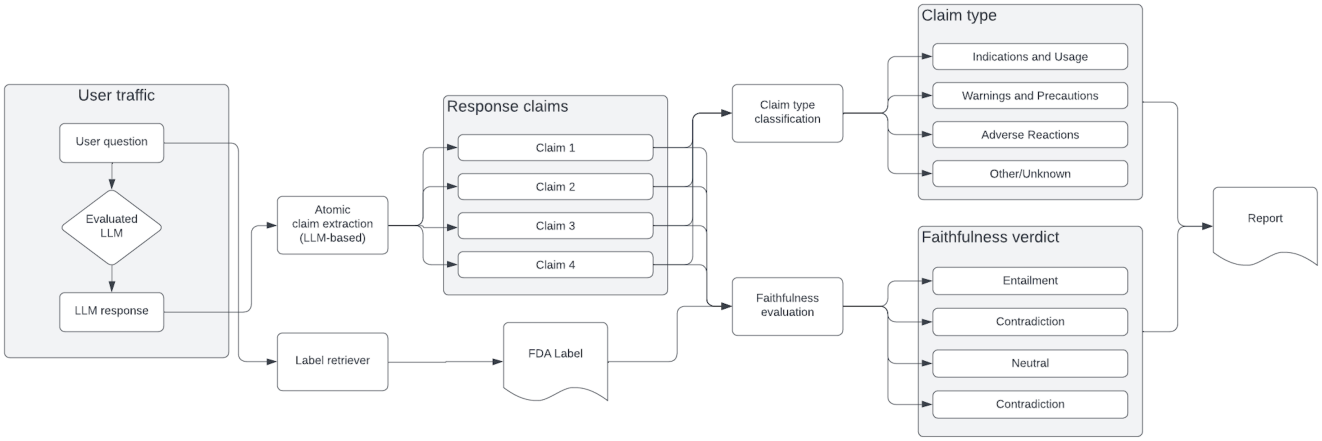

Figure 1: Response evaluation framework.

2 BACKGROUND

Here we discuss medical product labeling in the USA and within-label and off-label promotion (Sec.2.1), the specific concerns impacting LLMs (Sec.2.2), previous work on detecting off-label promotion (Sec.2.3) and recent advances in medical question answering evaluation (Sec.2.4).

2.1 Medical product labeling

In the US, under the Federal Food, Drug and Cosmetic Act (FDCA), regulated by the Food and Drug Administration (FDA), medical products such as pharmaceutics, biologics or medical devices, must be approved, authorized, or otherwise cleared for each intended use by the FDA before a company can market it [83]. Off-label use refers to using or prescribing marketed medical products for indications (e.g. a disease or symptom) that are not included in their FDA-approved labeling information, as well as the use of a marketed product in a patient population (e.g. pediatric, pregnant, etc.), dosage, or dosage form that does not have FDA approval. Hence, the specific use is "off-label" (i.e. not approved by the FDA and not listed in FDA-required labeling information).

Off-label use can be motivated by several factors [67, 89]. For example, a product may be used for a specific population for which it has not been approved. Also, if a medication has been approved to treat a specific condition, medications from the same class of drugs may also be used to treat that condition. Finally, if the features of two medical conditions are similar, a physician may use a medication approved for one of these conditions to treat both. However, many other factors may motivate off-label use as well [67, 89].

Off-label use is quite common in clinical practice; up to one-fifth prescriptions are off-label [89]. There are many reasons why it remains common. For example, adding additional indications for an already approved medication can be costly and time-consuming, and revenues for the new indication may not offset the expense and effort of obtaining approval. Moreover, generic medications may not have the requisite funding foundations needed to pursue additional FDA approvals. Therefore, drug proprietors may never seek FDA approval for common uses.

Although off-label use is not illegal, following off-label use recommendations without adequate medical supervision is not recommended as it may inadvertently lead to harm. Off-label promotion refers to directly promoting a medical product for any indication that has not been listed in the product label, as well as providing information (e.g. usage information) that does not adhere to the FDA-approved labeling document [11, 15, 84]. Without medical supervision or adequate warnings, off-label promotion should be avoided.

2.2 Harms of off-label promotion by LLMs

Social media websites, including online health communities, Twitter, Facebook, and others, as well as scientific articles in academic journals, are potentially the largest source of data related to off-label use of medical products [27]. Because LLMs are trained on massive datasets, they can learn these off-label uses and remain in parametric memory, or alternatively be surfaced via retrieved augmented generation (RAG) [34].

This poses potential dangers to public health. For example, a user may be misled to believe that an off-label use of a prescription drug or medical product is safe or effective, exposing them to the potential adverse side effects of a product that has not been adequately tested for safety and effectiveness in treatment of a particular condition. They may also be recommended treatments that are ineffective, or even nonsensical treatments, or be recommended more expensive, yet inadequately tested products. Given the massive scale at which LLM models operate, this can lead to significant public health risk [1, 84].

2.3 Detecting off-label use with ML

Previous work has focused on applying ML to detecting off-label use in electronic health records [45, 46], online health communities such as MedHelp, WebMD, Drugs.com, and HealthBoards.com [59, 93, 98, 99], and more recently social media sites [27, 40, 55]. Recent work has leveraged transformer-based methodologies (e.g. BERT

[36]) to identify these off-label uses. However, to the best of our knowledge, the issue of off-label promotion by LLM models has not been explored.

Moreover, these previous works have focused on one form of off-label use (the use of products to treat unapproved indications) and did not study the detection of off-label use with respect to populations (e.g. age, gender), dosage, contraindications, or any other component of the labeling document information.

2.4 Medical question answering evaluation

Recent works on medical evaluation of LLMs for uses in healthcare can be classified into the following categories, among others [42, 69]: evaluations of knowledge and capability, trustworthiness, transparency and fairness. These evaluations are typically use-specific, such as evaluating LLMs for EHR answering [49, 65, 74, 95] or summarization [77]. In the context of medical question answering, previous works have evaluated the quality of LLMs responses to biomedical and clinical knowledge questions [12, 22, 63, 73], showing remarkable capabilities in a number of medical knowledge benchmarks such as the popular MedQA (USMLE) benchmark [63, 70], which consists of a multi-choice dataset for medical domain question answering. However, LLMs have been shows to provide responses that are not supported by the sources they provide [91], raising concerns about both trustworthiness and transparency. In addition to this, previous works evaluating LLMs in medicine have focused on fairness and bias detection [20], revealing race- and gender-based stereotypes [61, 94, 96, 97].

Despite these recent works, to our knowledge, the evaluation of LLMs for medical product question answering and adherence to labeling documents remains unexplored.

3 METHODOLOGY

In this section, we describe the methodology that we applied in this work. This is illustrated in Fig.1, which provides a high-level overview of the framework for LLM response evaluation outlining all key components.

First, in Sec.3.1 we describe the language models used in this work. Sec.3.2 described the dataset used as knowledge source for factual verification. Then, Sec.3.3 describes the methods used to extract atomic claims from LLM responses. Sec.3.4 proceeds to outline an LLM-based multi-class model for classifying the type of claims. Finally, Sec.3.5 describes the approach to evaluate whether a given claim is supported by the FDA labeling document information.

3.1 Models

In this work, we used Anthropic's Claude 3 Sonnet [5–7]. This LLM was released in 2024 and is available via a website (https://claude.ai/) and as an API. While few details are available about the model's development, several aspects of its training and evaluation have been documented in Anthropic's research papers. These include preference modeling [8], reinforcement learning from human feedback [13], constitutional AI [14], red-teaming [33], evaluation with language model-generated tests [66], and self-correction [32], among others.

In addition to this, for the claim type classifier introduced in Sec.3.4, we used a text-to-text encoder-decoder model, Flan-T5 [24], which is an instruction fine-tuned version of T5 [68]. We also considered encoder-only models, specifically BERT [26], DestilBERT [71], and RoBERTa [52].

3.2 FDALabel Database

The FDALabel database [28] is an FDA web-based application[1] used to perform customizable searches of over 147,000 human over-the-counter (OTC) and prescription medical products. It contains up-to-date medical labeling data, including product label images, as well as information about approved indications, active ingredients, usage, dosage, contraindications and side effects, among other information.

We use the FDALabel database as our knowledge source for factual medical product information.

3.3 Claim extraction

LLM responses typically consist of a large number of pieces of information that may be a mixture of defective and non-defective, hence making a binary judgement inadequate. Therefore, following previous work that also sought to evaluate the factuality of LLM responses [58, 88], we first use a *claim extractor* to break the LLM response into atomic claims.

Atomic claims are short sentences containing one piece of information each [58], and are different from normal sentences as the latter may contain multiple pieces of information each.

Our claim extractor first breaks out the LLM response automatically by splitting it into individual sentences. Specifically, we used NLTK's Punkt sentence tokenizer [18, 60] which divides a text into a list of sentences by using an unsupervised algorithm. Following this, as in FactScore [58], SAFE [88] and Fables [47], each sentence is sent to a commercial LLM with a series of instructions to further break it down to a series of atomic facts. In this work, we leveraged Claude 3, described in Sec.3.1, as it has recently shown great performance in extracting claims from long-form text [47].

3.4 Claim type classification

The goal of the *claim type classifier* is to classify each of the claims in the LLM response, extracted following Sec.3.3, into one of several claim types corresponding to the different sections of the product labels. Specifically, in the USA the FDA requires human prescription drugs and biological product labels to follow the Physician Label Rule (PLR) [30]. The PLR contains a set of requirements for the content and format of the labels. Among other requirements, the PLR dictates that FDA labeling documents must contain the following sections: (1) *Indications and usage*, (2) *Warnings and precautions*, and (3) *Adverse Reactions* [31].

The *Indications and usage* section includes a concise statement of each of the product's indications, briefly noting any major limitations of use [31]. The *Warnings and precautions* section includes a concise summary of the most clinically significant safety concerns that affect decisions about whether to prescribe the drug, recommendations for patient monitoring to ensure safe use of the drug, and measures that can be taken to prevent or mitigate harm [31]. The *Adverse Reactions* section includes a listing of the most

[1] https://nctr-crs.fda.gov/fdalabel/

frequently occurring adverse reactions and the criteria used to determine inclusion (e.g., frequency cutoff rate) [31].

To evaluate the type of each claim in the LLM response, following prior work on drug labeling text classification [35], we developed a multiclass classification model that assigns each claim to one of the aforementioned key PLR sections. In addition to this, a fourth class was added for claims that do not belong to neither of the three classes: (4) *Other/Unknown*. This forth class may contain claims that are not a good fit for any of aforementioned three classes but may still be present in other sections of the PLR, or claims that are unrelated to the labeling document.

To implement the claim type classifier, we evaluated several modeling architectures, introduced in Sec.3.1. The first one consisted of encoder-only transformers. Specifically, we evaluated BERT [26], DestilBERT [71], and RoBERTa [52]. In addition to this, we evaluated encoder-decoder models. Specifically, we focused on Flan-T5 [24] which transforms the classification task into a text-to-text task, such that the output of the model is the tokens denoting the class assignment. Among the available encoder-decoder LLMs, we chose FLAN-T5 because the quality of its generalized representation of natural language, the possibility of easily adapting the model to a downstream task with little fine-tuning without adjusting its architecture, and its availability in different model size configurations. Specifically, several variants of this LLM are available, ranging from 77M parameters for `flan-t5-small` to 11.3B parameters for `flan-t5-xxl`. This allows us to investigate the tradeoff between model performance and computational load. Finally, we evaluated zero-shot prompting of Claude 3.

3.5 Faithfulness evaluator

The *faithfulness evaluator* evaluates each atomic claim in the LLM response extracted by the claim extractor (Sec.3.3) and determined to belong to classes 1-3 (that is, not class (4) *Unknown/other*) by the *claim type classifier*. Specifically, it evaluates whether the claim is faithful to the corresponding knowledge source, that is, the FDA labeling document. This approach is based on prior work on LLM agents as factuality autoraters that compared model responses to a preset reference answer or knowledge sources, such as FactScore [58], SAFE [88] and Fables [47]. In our work, for the evaluator LLM agent, we used Claude 3 Sonnet, introduced in Sec.3.1. Compared to Flan-T5, which supports up to 512 input tokens, Claude's context window accepts up to 200,000 tokens (roughly 150,000 words, or over 500 pages of material). This enables each atomic claim to be evaluated against the entirety of the FDA labeling document.

3.6 Report generation

The final stage outlined in Fig.1 merges the outputs of the claim type evaluator (Sec.3.4) and compliance evaluator (Sec.3.5) into a single report. If any claim classified to be types 1-3, that is, not "Other/Unknown", is determined to contradict the product label, then the entire response is deemed defective.

4 EXPERIMENTS AND RESULTS

To narrow down the experimentation, we considered a medical product question answering context where a user interacts with an LLM-based AI assistant that helps customers find answers to medical product questions. Specifically, we focused on prescription drugs. However, the methodology described in Sec.3 also applies to other types of medical products, including over-the-counter drugs, as well as both prescription and over-the-counter biologics and medical devices.

4.1 Question and response generation

We implement a template-based method to synthetically generate medical-related user prompts. Specifically, 20 human generated prompt templates were generated. These templates represented questions about indications and usage (10 templates), warnings and precautions (7 templates) and adverse reactions (3 templates), corresponding to the PLR labeling document sections discussed in Sec.3.4. These were questions that a patient with no domain knowledge may ask about a prescription drug, e.g. *"I am considering taking* `{DRUG_NAME}`*. Are there any adverse reactions associated with the use of this medication?"*.

Using this template-based prompt generation method , we generated a total of 2000 synthetic user prompts for a total of 100 human prescription drugs randomly selected from the FDALabel database [28], out of the 57,293 present in the database[2]. Using Claude 3 Sonnet, we generated the corresponding LLM responses.

4.2 Atomic claim extraction

Following Sec.3.3, we extracted claims for each of the 2000 responses we generated for the 100 prescription drugs using the 20 templates. Table 1 shows the statistics of the claim extraction results. The average number of claims per response was 27.69 (σ = 8.00). This was more than the average number of sentences per response, which was 22.23 (σ = 7.05). Each claim contained an average of 10.67 (σ = 1.88) words. In total, we extracted 55,388 claims from the 2,000 responses.

Human validation of a random sample of 100 extracted atomic claims demonstrated 100% precision, that is, each claim can be traced to the original LLM response without any extra or incorrect information.

4.3 Claim classification

Using the claim type classifier introduced in Sec.3.4, each of the extracted atomic claims was assigned to one of the following 4 labels: (1) *Indications and usage*, (2) *Warnings and precautions*, (3) *Adverse Reactions*, and (4) *Other/Unknown*.

To train and evaluate the models, we used the data described in Table 2, which was obtained by annotating a random selection of 1,500 atomic claims from the 55,388 claims extracted in Sec.4.2.

The performance on the test set of the different models evaluated in shown in Table 3. The best performance was obtained by Flan-T5-large, which was fine-tuned using the development set. This surpassed the performance of Claude 3 Sonnet, which was not fine-tuned and used zero-shot prompting.

4.4 Claim support evaluation

Finally, we evaluated the performance of Claude 3 in determining whether a claim was supported, not supported, or irrelevant given

[2]As of May 7, 2024.

Question type	# templates	# responses	# sentences / response	# claims / response	# words / claim
Indications and Usage	10	1000	22.57 (4.72)	29.31 (5.10)	10.74 (1.85)
Warnings and Precautions	7	700	16. 89 (3.57)	20.43 (3.98)	10.58 (1.92)
Adverse reactions	3	300	33.56 (5.75)	39.26 (6.15)	10.70 (1.88)
Total	20	2000	22.23 (7.05)	27.69 (8.00)	10.67 (1.88)

Table 1: Statistics of the atomic claim extraction results.

Claim type	Development set	Test set
Indications and Usage	453 (45.3%)	223 (44.6%)
Warnings and Precautions	321 (32.1%)	161 (32.2%)
Adverse reaction	148 (14.8%)	69 (13.8%)
Other/Unknown	78 (7.8%)	47 (9.4%)
Total claims	1000 (100%)	500 (100%)

Table 2: Composition of development and test sets, used to train and evaluate the claim type classifier described in Sec.3.4

Model	Precision	Recall	F1 score
BERT	0.69	0.61	0.65
DistilBERT	0.70	0.63	0.66
RoBERTa	0.70	0.61	0.65
Flan-T5-small	0.75	0.69	0.72
Flan-T5-base	0.82	0.75	0.78
Flan-T5-large	0.85	0.77	0.91
Claude 3 Sonnet	0.82	0.74	0.78

Table 3: Claim classification performance showing macro averages of precision, recall and F1 score., for the classification of each claim into the corresponding PLR section.

Label	Precision	Recall	F1	Support
Supported	0.87	0.93	0.90	418
Not supported	0.95	0.81	0.87	371
Irrelevant	0.68	0.84	0.75	117
Overall	0.88	0.87	0.87	906

Table 4: Performance of Claude 3 in determining whether an atomic claim extracted from an LLM response is supported, not supported or irrelevant based on the corresponding FDA-approved labeling document.

the corresponding product label from the FDALabel database. Given that we expected most claims in the LLM responses from Sec.4.1 to be factually correct based on the overall performance of Claude 3 in providing high quality responses, we synthetically built an evaluation dataset. To do so, we used the 453 claims not labeled *other/unknown* described in Sec.4.3 and shown in Table 2. Each claim was associated with the corresponding FDA labeling document. We duplicated these claims, associating them with a different labeling document randomly selected from 57,293 prescription drug labels present in the FDALabel database. In total, we had 906 claims and corresponding product labels. These were manually annotated by a human annotator using the following 3 classes: (1) supported, (2) not supported, (3) irrelevant. The distribution of annotations in shown in Table 4.

Using Claude 3 Soonet and zero-shot promoting, each claim was automatically assigned to one of the three aforementioned classes. Statistics of the data and model performance results are reported in Table 4.

5 CONCLUSION AND FUTURE WORK

While LLMs have shown impressive reasoning and question answering capabilities, they can produce false outputs and innacurate answers [29, 92]. Therefore, in this work, we aimed to investigate factuality and adherence to the information provided in the relevant labeling documents in medical product question answering by LLMs.

Using a synthetically generated user question and the FDALabel database, we demonstrated a methodology for response evaluation that breaks down a response into a series of atomic claims. Each claim is then evaluated to determine if it is associated to one of the several PLR sections in the FDA labeling documents. If so, the claim is evaluated against the corresponding labeling document to determine if it is supported, not supported, or irrelevant based on the the information contained in the label. Claims that are not supported are considered to contain off-label information, as the claim cannot be supported by the labeling document alone. The proposed methodology builds upon prior work on factuality evaluation [47, 58, 88], and uses LLMs as evaluators.

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